38. (New) The method according to Claim 32, wherein the treatment of the racemic lactam is conducted at a temperature of 10 to 60°C.

39. (New) The method according to Claim 32, wherein each of the optically active compounds of formulae I and II is isolated after formation.

REMARKS

This is in response to the Official Action mailed June 12, 2003 for the above-captioned patent application. Claims 1-16 are pending in the application. Claims 10 and 11 are withdrawn from consideration. Claims 1-9 and 12-16 are rejected under 35 U.S.C.§ 102(a). Applicants have amended the rejected claims to specify that the nucleophile to be used is a C1-10 nucleophile. Support for amendment of the claims can be found p.3, lines 4-6 of the specification. No New matter is introduced by the amended claims. For reasons set forth in detail below, Applicants request that all rejections be withdrawn and that the pending claims be allowed.

1. Objections

The amendment filed March 11 2003, is objected to under 35 U.S.C., § 132. The Examiner alleges that the amendment introduces new matter into the disclosure of the invention. In particular, the Examiner maintains that there is no clear basis or support found in the present specification for the changes requested to the specification in the paragraph beginning at page 3, two lines from the bottom.

Applicants assert that the amendment at page 3, two lines from the bottom, was made to correct the designation of the compound of formula II. The correct designation of the formula II compound is (1S, 4R)-4-amino-2-cyclopentene-1-carboxylic acid derivatives, rather than (1S, 4R)-4-amino-2-cyclopentene-1-carboxylic acid derivatives. Specifically, the compound of formula II wherein R^1 is acetyl and R^2 is hydrogen (see p. 3, last two lines of the specification) should be designated (1S, 4R)-4-acetylamino-2-cyclopentene-1-carboxylic acid and not (1S, 4R)-1-acetylamino-2-cyclopentene-4-carboxylic acid. Applicants assert that the amendment is necessary to conform the designation of the compound of formula II to the actual formula. Thus, no new matter is added.

2. Claim Rejections under 35 U.S.C. §102

Claims 1-9 and 12-16 have been rejected under 35 U.S.C. §102(b) as anticipated by Dawson et al. (WO99/10519; "Dawson").

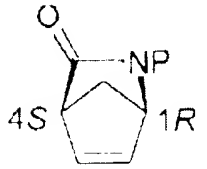
According to the Examiner, the claims are directed to the hydrolysis of a substituted-2-azabicyclo[2,2]hept-5-ene-3-one, wherein the substituent is acyl, alkoxycarbonyl or aryloxycarbonyl, using a hydrolase such as an acylase followed by a subsequent reduction of the product.

The Examiner alleges that Dawson teaches the hydrolysis of at least racemic tert-butyl-3-oxo-2-azabicyclo[2,2]hept-5-ene-3-one and 2-acetyl-2-azabicyclo[2,2]hept-5-ene-3-one using a hydrolase such as acylase with an effective amount of nucleophile and base at constant pH. The optically active compound of formula II is inherently produced. The Examiner maintains that Dawson further teaches the subsequent reduction of said compound using a metal

hydride. The enzyme used by Dawson, *i.e.*, savinase, is a serine protease and is the same as subtilisin.

Applicants respectfully submitted that the pending claims are not anticipated by Dawson. Anticipation under 35 U.S.C §102 requires that "all the elements and limitations of the claim be found within a single prior art reference...there must be no difference between the claimed invention and the reference disclosed, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.* 927 F2d 1565, 18 U.S.P.Q. 2d 1001, 18 U.S.P.Q. 2d 1896 (1991). *See also* MPEP 706.02 ("For anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention...").

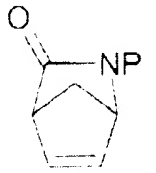
Applicants assert that Dawson describes a process for the preparation of substantially enantiomerically pure *N*-protected (1*R*, 4S)-2-azabicyclo[2.2.1]hept-5-en-3-one of the formula:



IV

wherein P is an activating and protecting group,

wherein a racemic mixture of *N*-protected racemic 2-azabicyclo[2.2.1]hept-5-en-3-one of the formula:



V

wherein P is an activating and protecting group,

is treated with an acylase enzyme and the unreacted enantiomer of formula (IV) is isolated from the reaction mixture by conventional techniques (see, claim 1).

As set forth in Dawson, a preferred activating/protecting group is an acyl or substituted oxycarbonyl group. Preferred acyl groups include formyl or lower alkanoyl, especially acetyl. Preferred substituted oxycarbonyl groups are of the formula ROC(O)-, wherein R is alkyl or aralkyl. A preferred alkyl group is *tert*-butyl. A possible aralkyl group is benzyl (page 3, last line to page 4, line 8 of Dawson).

Further, it is preferred that the reaction is carried out in a mixture of organic solvent and water. It is preferred to use water miscible organic solvents such as cyclic ethers, e.g., tetrahydrofuran or 1,4-dioxan (page 4, lines 12 to 16).

As disclosed by Dawson, the substantially enantiomerically pure *N*-protected (1R, 4S)-2-azabicyclo[2.2.1]hept-5-en-3-one of the formula IV may be directly converted into the corresponding ring-opened amino alcohol of the formula

VI

by using sodium borohydride (page 6, lines 25 to 28).

Applicants have amended claims 1-8 (new claims 17-24) to specify that the nucleophile to be used is a C_{1-10} nucleophile, thus, the subject matter encompassed by the pending claims refers to a process for the formation of optically active *N*-protected 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives wherein the biotransformation is performed in the presence of a C_{1-10} alcohol. Although Dawson discloses the presence of an organic solvent, he does not disclose using a C_{1-10} alcohol as the organic solvent. Thus, new claims 17-24 are not anticipated by Dawson.

Furthermore, the last step of the process of Claim 9 (new claim 25) is a hydrolysis of the compound of the formula

IV

to a compound of the formula

V

Dawson fails to disclose such a hydrolysis step. Therefore, Claim 9 (new claim 25) and new claims dependent thereupon, cannot be anticipated by Dawson.

MISCELLANEOUS

New Claim 32 refers to a process for the formation of optically active *N*-protected 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives wherein the *N*-protecting group is C_{1-4} alkanoyl which is substituted with one or more halogen atoms, benzylcarbonyl, phenylcarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl or phenyloxycarbonyl.

Dawson fails to disclose such protecting groups. Therefore, new Claim 32 and claims dependent thereupon are not anticipated by Dawson.

CONCLUSION

Entry of the foregoing remarks into the file history of the above identified application is respectfully requested. Applicants believe that the invention described and defined by the claims is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

Dated: September 26, 2003

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